Remarks

Status of the Claims and Support for the Amendments to the Claims and Specification

By the foregoing amendments to the specification, Applicants have replaced the trademarks in the present specification with capitalized designations for the trademarks, and also included generic terminology for the trademarks. Applicants submit that these amendments introduce no new matter, particularly since these amendments were required by the Examiner (see Office Action of May 3, 2007, at page 2), and their entry is respectfully requested.

By the foregoing amendments, claims 1, 14, 15 and 16 are sought to be amended, and claims 19-22 are sought to be added. Claims 2-4 and 17 have been canceled without prejudice or disclaimer. Support for the amendments to the claims and the new claims, can be found throughout the present specification, for example in paragraph [0060] - [0061], throughout Example 3 at pages 15-16, paragraphs [0063] - [0070], and in the abstract. Therefore, these amendments introduce no new matter.

Upon entry of the foregoing amendments, claims 1, 5-16 and 18-22 are pending in the application, with claims 1 and 16 being the independent claims.

Summary of the Office Action

In the Office Action dated May 3, 2007, the Examiner has made one objection to, and two rejections of, the claims. Based on the following remarks, Applicants respectfully

request that the Examiner reconsider the outstanding objection and rejections and that they be withdrawn.

Identification of Trademarks in the Specification

In the Office Action at page 2, section 2, the Examiner notes that the present specification contains various trademarks. The Examiner has requested that these trademarks be capitalized and accompanied by the generic terminology when they appear in the specification. By the foregoing amendments to the specification, trademarks have been replaced with capitalized designations for the trademarks, and generic terminology has also been included. Hence, this portion of the Office Action has been accommodated.

The Rejection Under 35 U.S.C. § 103(a) over Mascarenhas in view of Jang, and Darmon

In the Office Action at pages 3-4, the Examiner has rejected claims 1 and 15 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Mascarenhas (U.S. Patent No. 6,887,851; hereinafter "Mascarenhas") in view of Jiang *et al.* (*Int. J. Cancer 91:* 173-179 (2001); hereinafter "Jiang") and Darmon *et al.* (*Nature 377*:445-448 (1995); hereinafter "Darmon"). Applicants respectfully traverse this rejection.

The Examiner contends that Mascarenhas discloses that treatment of mice with adenocarcinomas with insulin-like growth factor binding protein-3 (IGFBP-3) and doxorubicin increased caspase 3 activity compared to normal controls. The Examiner notes that Mascarenhas does not disclose an increase in the amount of the cleaved 17 kDa fragment of caspase 3. The Examiner relies on the disclosures of Jiang and Darmon to cure

this deficiency. Specifically, the Examiner notes that Jiang discloses that an increase in caspase 3 activity was the result of cleavage of pro-caspase 3 into a 12 kDa and a 17 kDa fragments. The Examiner notes that Darmon discloses that the pro-caspase 3 is an inactive precursor. The Examiner therefore concludes:

> It would have been *prima facie* obvious to combine Mascarenhas treatment and detection of apoptosis by caspase 3 activity with Jiang *et al.* method of measuring apoptosis by caspase 3 activity to measure caspase 3-dependent apoptosis in a different manner;

Office Action, Page 4, 3rd full paragraph. Applicants respectfully disagree with the Examiner's contentions and conclusions.

Present claim 1 (and hence, claim 15 that depends ultimately therefrom) recites a method for evaluating the efficacy of a therapeutic agent that stimulates apoptosis in the body of a mammal. The method comprises obtaining a first sample of whole blood, plasma or serum, that can contain the 17 kDa fragment of caspase 3, prior to administration of the therapeutic agent, purifying this first sample using column chromatography to remove interfering components and assaying the first sample to determine the amount of the 17 kDa fragment of caspase 3 present. The therapeutic agent is then administered, and a second sample of whole blood, plasma or serum, is obtained, purified using column chromatography to remove interfering components and assayed to determine the amount of the 17kDa fragment of cleaved caspase 3 present in the second sample. An increase in the amount of the 17 kDa fragment measured in the second sample over the amount measured in the first sample indicates apoptosis stimulation and efficacy of the therapeutic agent.

Applicants respectfully submit that none of the references cited by the Examiner, alone or in combination, discloses assaying the amount of the 17 kDa fragment of the cleaved caspase-3 polypeptide from whole blood, plasma or serum, nor do they disclose purification using column chromatography of whole blood, plasma or serum samples prior to assaying the amount of the 17 kDa fragment of the cleaved caspase-3 polypeptide.

As set forth in *Graham v. John Deere Co. of Kansas City*, "[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966). Applicants respectfully submit that the differences between the presently claimed invention and the references cited by the Examiner are so great that it would not have been obvious to combine the various citations, as required by the Examiner, in order to render the presently claimed invention obvious. Furthermore, as set forth in *Graham*, and as reaffirmed more recently by the U.S. Supreme Court, courts are "to look at any secondary considerations that would prove instructive," when considering the obviousness of an invention. *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1729-1730 (2007).

Mascarenhas discloses assaying adrenocarcinoma homogenates using an enzymatic assay (Mascarenhas, Example 1, column 24, line 16) to determine the presence of caspase 3. As the Examiner notes, Mascarenhas does not detect the amount of the 17 kDa fragment of caspase 3. Jiang and Darmon disclose assaying for the 17 kDa fragment of caspase 3 in cultured cell homogenates, not whole blood, plasma or serum. Applicants submit that one

of ordinary skill in the art would not have combined the disclosure of Mascarenhas with that of Jiang or Darmon, in order to render obvious the presently claimed invention. Specifically, Applicants submit that there is no disclosure of detection of the amount of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum as recited in the presently claimed inventions in any of the references cited by the Examiner. Moreover, use of the methods of Jiang or Darmon to measure the levels of caspase 3 in whole blood, plasma or serum would have been fruitless for several reasons.

First, Applicants submit that, as disclosed in the present application and as embodied in the presently claimed invention, detection of the amount of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum, was not possible prior to the presently claimed invention, and as set forth below, was a surprising and unexpected result.

Applicants have unexpectedly discovered that it is possible to determine the amount of cleaved 17 kDa fragment of caspase 3 in whole blood, serum or plasma. Attached herewith as Exhibit B, and described in the attached declaration of Kathleen F. Pirollo, is experimental data from Applicants' laboratory, determining the amount of the 17 kDa fragment of caspase 3 in serum using Western blotting. Whole blood, plasma and serum contain many components, such as porphyrins and other components, that interfere with detection of the 17 kDA fragment of caspase 3. As detailed in the attached declaration and Exhibit B, the amount of the 17 kDa fragment of caspase 3 could not be determined (panel A) absent purification using column chromatography to remove interfering components, such as porphyrins (panel B). Applicants submit that it was unexpected that simply purifying whole blood, plasma or serum, using column chromatography would allow

for the detection of the cleaved 17 kDa fragment of caspase 3. The references cited by the Examiner, whether alone or in combination, would not have allowed a skilled artisan to determine the amount of 17 kDa fragment of caspase 3 in whole blood, plasma or serum (*See* Exhibit B, panel A), as there would not have been a reasonable expectation of success in making this determination. *See PharmaStem Therapeutics inc. v. ViaCell Inc.,* 491 F.3d 1342, 1360 (Fed. Cir. 2007) (stating that invalidity under obviousness requires a showing that "a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so."). A person of ordinary skill in the art, at the time of filing of the present application, would not have been able to detect the amount of the 17 kDa fragment of caspase 3 from whole blood, plasma or serum, due to the presence of interfering components, such as porphyrins. There was no reasonable expectation that detection of the amount of the 17 kDa fragment of caspase 3 from whole blood, plasma or serum would have been successful based on the disclosures of Mascarenhas, Jiang and Darmon, alone or in combination, as none of these references disclose or suggest purification using column chromatography. Therefore, these references do not establish a *prima facie* case of obviousness.

Mascarenhas is limited to the use of enzymatic techniques to determine the *presence*, not the *amount*, of caspase 3. Furthermore, while Jiang and Darmon may disclose determining the amount of the 17 kDa fragment of caspase 3, these reference are limited to detection in cell homogenates and not in blood, plasma or serum, which as noted above, cannot be assayed without first being purified using column chromatography to remove

interfering components, such as porphyrins. Thus, applicants submit that it would not have been obvious, or even obvious to try, to combine the disclosure of Mascarenhas with the disclosures of Jiang and Darmon to determine the amount of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum, as a person of ordinary skill in the art would not have considered it possible to perform such an assay in such samples. As set forth above, it was only after the unexpected results demonstrated by Applicants that such an assay could have been performed.

In view of the foregoing remarks, Applicants respectfully submit that the Examiner has not established a p*rima facie* case of obviousness. Reconsideration and withdrawal of the rejection of claims 1 and 15 under 35 U.S.C. § 103(a) are therefore respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Mascarenhas in view of Xu

In the Office Action at pages 4-5, the Examiner has rejected claims 5-14 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Mascarenhas in view of Xu *et al.* (*Molecular Cancer Therapeutics 1*:337-346 (2002); hereinafter "Xu"). Applicants respectfully traverse this rejection.

As discussed above, Mascarenhas discloses assaying adrenocarcinoma homogenates using an enzymatic assay (*See* Mascarenhas, Example 1, column 24, line 16). The Examiner notes that the enzymatic assay of Mascarenhas does not assay the amount of the 17 kDa fragment of caspase 3. In addition, the Examiner notes, Mascarenhas does not disclose the targeted cationic lipid gene delivery system disclosed in the presently claimed

invention. The Examiner states that Xu discloses a method of systemic p53 gene therapy comprising administering a targeted cationic liposome in combination with docetaxel, and goes on to state that:

> One of skill in the art would have been motivated to apply Xu *et al.'s* systemic p53 gene therapy to Mascarenhas' treatment and detection of apoptosis by *caspase 3 activity* because Xu disclosed that sensitization of breast tumors to chemotherapeutic agents is due to the restoration of the apoptotic pathway. It would have been *prima facie* obvious to combine Mascarenhas treatment and detection of apoptosis by caspase 3 activity with Xu's systemic p53 gene therapy to measure apoptosis following the p53 gene therapy treatment.

Office Action, Page 5, 4th full paragraph [Emphasis Added]. Applicants respectfully disagree with the Examiner's contentions and conclusions.

Applicants respectfully submit that neither Mascarenhas nor Xu, alone or in combination, disclose assaying the *amount* of the 17 kDa fragment of the cleaved caspase-3 polypeptide from whole blood, plasma or serum, nor do they disclose purification of whole blood, plasma or serum samples using column chromatography prior to assaying the amount of the 17 kDa fragment of the cleaved caspase-3 polypeptide.

As discussed above, Mascarenhas discloses measuring caspase 3 activity to determine the *presence* of this enzyme in mouse adrenocarcinomas tissue homogenates using an enzymatic assay, while the presently claimed invention requires determining the *amount* of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum. Therefore, Mascarenhas does not disclose the presently claimed invention. Furthermore, Applicants note that it would not have been obvious to try to determine the amount of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum, as discussed above.

Applicants respectfully submit that, even assuming that Xu discloses a method of systemic gene therapy comprising administering a targeted cationic liposome complex, it would not have been obvious to assay the *amount* of the 17 kDa fragment of caspase 3 following treatment with such liposome complexes based on the disclosures of Mascarenhas or Xu, alone or in combination. Absent the present application, and as evidenced in the declaration of Kathleen F. Pirollo and in Exhibit B, a person of skill in the art would not have been able to assay the *amount* of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum (*See* Exhibit B, panel A). As set forth in Exhibit B, detection of the 17 kDa fragment of caspase 3 was not possible absent purification using column chromatography required by the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully submit that the Examiner has not established a p*rima facie* case of obviousness. Reconsideration and withdrawal of the rejection of claims 1 and 15 under 35 U.S.C. § 103(a) are therefore respectfully requested.

Objection to claims 2-4

The Examiner has objected to claims 2-4 as being improperly dependent upon a rejected claim. Applicants thank the Examiner for the identification of this provisionally allowable subject matter. By the foregoing amendments, claims 2-4 have been cancelled, thus rendering the Examiner's objection moot.

Allowance of claims 16-18

In the Office Action at page 6, the Examiner notes that no disclosure renders claims 16-18 unpatentable. Applicants thank the Examiner for the identification of this allowable subject matter. However, in view of the foregoing remarks, Applicants respectfully submit that all of the claims as currently presented are allowable, early notification to this effect is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, rendered moot or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and objections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Date: Oct. 3, 2007

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